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Short Communication: The Veterans Aging Cohort Study Index Is an Effective Tool to Assess Baseline Frailty Status in a Contemporary Cohort of HIV-Infected Persons

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Abstract

The Veterans Aging Cohort Study (VACS) Index has previously been used to identify frail HIV-infected persons. However, data demonstrating the independent association between the VACS Index and baseline frailty status is lacking. Furthermore, the ability of the VACS Index to also reflect transitions in frailty status over time is unknown. We used data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study) to determine independent association of baseline frailty status with the VACS Index. We also evaluated VACS Index changes with frailty status transitions over time. We included 303 participants (median age 48 years, 76% men, 57% non-Hispanic white, 91% with plasma HIV RNA <400 copies/ml, and median $CD4^+$ cell count 595 cells/ml) with baseline and follow-up frailty assessments and used the Fried's criteria to define frailty status. There were 184 (61%) nonfrail, 112 (37%) prefrail, and seven (2%) frail participants at baseline. Prefrail/frail participants had significantly higher median VACS Index scores compared with nonfrail participants (18 versus 10, $p<0.001$). In multivariable analysis, prefrailty/frailty was independently associated with a higher VACS Index score (odds ratio 1.025, $p=0.019$). After a median follow-up of 12 months, participants who remained prefrail/frail compared to those who remained nonfrail continued to have higher median VACS Index scores. The VACS Index score did not significantly change with transitions in frailty status over time. Our study highlights the potential utility of the VACS Index in frailty assessment within the clinical setting.

Frailty is a clinical syndrome resulting from dysregulation of multiple physiologic systems that leads to low endurance, poor strength, low physical activity, increased hospitalization, and mortality.[1] Studies derived from the Multicenter AIDS Cohort Study (MACS) have shown that frailty occurs at a much younger age among HIV-infected persons compared with demographically matched HIV-uninfected individuals.[2,3] Among the aging HIV-infected population, in whom frailty prevalence has been estimated to range from 2% to 20%[4] the role of chronic inflammation in the multifactorial pathogenesis of this syndrome is increasingly recognized.[4] Frailty has previously been shown to be independently associated with low $CD4^+$ cell count, higher plasma HIV RNA, longer duration of HIV infection, previous history of opportunistic infections, and depression.[2,4]

The Veterans Aging Cohort Study (VACS) Index is a multivariable risk assessment tool that has been shown to accurately predict 5-year all-cause mortality risk among HIV-infected persons.[5] It has also been shown to predict morbidity, including hospitalizations and medical intensive care unit admissions,[6] and correlate with HIV-related chronic inflammation.[7] Because frailty and the VACS Index predict the same outcomes, the VACS Index has been used in two recent studies as a surrogate marker to identify frail HIV-infected persons.[8,9] Another study has also shown that the median VACS Index scores of frail HIV-infected persons were significantly higher compared to nonfrail individuals.[10] Despite these data, the association of the VACS Index with frailty independent of other frailty predictors has not yet been demonstrated. Furthermore, it is unknown whether

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transitions in frailty status over time could also be reflected by changes in the VACS Index.

In this study, we determined the independent association of the VACS Index score with frailty as defined by the Fried's criteria, the most widely accepted definition of frailty.[1] Furthermore, we evaluated the dynamics of the VACS Index with changes in frailty status over time.

We used data from the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN Study), an observational cohort funded by the Centers for Disease Control and Prevention (CDC). The SUN Study design has been previously reported.[11] Briefly, 700 participants from seven HIV clinics in four cities in the United States (Saint Louis, Denver, Minneapolis, and Providence) were enrolled from March 2004 to June 2006 and followed until June 2012. Participants were recruited if they were naive to, or had previously received combination antiretroviral therapy (cART). Frailty assessments were performed from June 2010 to May 2012. Participants with initial and follow-up frailty assessments were included. Participants with missing frailty assessments and incomplete VACS Index information were excluded.

Nonfrail, prefrail, and frail states were defined by the presence of 0, 1–2, and ≥3 of five established criteria (unintentional weight loss, physical inactivity, exhaustion, weak grip strength, and slow walking time), respectively[1] (Table 1). All study coordinators were trained to conduct the frailty assessment uniformly. The VACS Index, which utilizes HIV-related and unrelated variables (Table 2), was calculated for all participants during the initial and follow-up frailty assessments.

Previous frailty studies have shown that prefrailty is an intermediary in the spectrum of nonfrailty through frailty and the majority of persons pass through this stage before transitioning to a frail or nonfrail state both in the HIV-infected[4] and HIV-uninfected population.[12] Because of the low prevalence of frailty in our cohort, we combined prefrail and frail states to increase statistical power. Association of the VACS Index and its components with prefrail/frail status at baseline and at follow-up assessments was determined using the χ^2 test for categorical variables and the Student's *t*-test or the Wilcoxon rank-sum test for continuous variables depending on whether variables were normally distributed or not. To address multiple comparisons, we used the Bonferroni method and determined that comparisons with p values < 0.006 were statistically significant.

We then assessed by univariate and multivariable analysis the association of the VACS Index and several HIV-related and unrelated variables with prefrail/frail status. Associations in univariate analysis with $p < 0.10$ were then modeled using stepwise logistic regression for the outcome of prefrailty/frailty; for this analysis, p values < 0.05 were considered statistically significant. All analyses were conducted using SPSS version 22.

Evaluations of 303 participants were available for analysis. The median age was 48 years [interquartile range (IQR) 42–54 years], 76% were men, 57% were non-Hispanic white, 93% were prescribed cART, 91% had a plasma HIV RNA <400 copies/ml, and the median baseline $CD4^+$ cell count was 595 cells/ml (IQR 441–782 cells/ml). Since frailty assessments were conducted only from 2010 to 2012, the majority of the participants excluded from this analysis had

Table 1. Fried's Criteria with Modification of Assessment of Physical Activity

Criteria	*Definition*			
Unintentional weight loss[a]	>10 pound weight loss documented in the last year or ≥5% of the previous body weight			
Physical inactivity	Subjects answering 3 when asked whether their health limits vigorous activities such as running, lifting heavy objects, participating in strenuous sports: 1 = not at all, 2 = yes, limited a little, or 3 = yes, limited a lot			
Exhaustion	Subjects answering 2 or 3 to either one of two statements: How often have you felt that: (a) everything you did was an effort or (b) I could not ''get going'' 0 = rarely (<1 day), 1 = some of the time (1–2 days), 2 = occasionally (3–4 days), or 3 = most of the time (5–7 days)			
Weak grip strength	*Male*		*Female*	
	BMI kg/m²	*kg*	*BMI kg/m²*	*kg*
	≤24	≤29	≤23	≤17
	24.1–26.0	≤30	23.1–26.0	≤17.3
	26.1–28.0	≤30	26.1–29.0	≤18
	>28	≤32	>29	≤21
Slow walking time	*Male*		*Female*	
	Height (cm)	*Seconds*[b]	*Height (cm)*	*Seconds*
	≤173	≥7	≤159	≥7
	>173	≥6	>159	≥6

[a]For patients who had attended clinic for <12 months, unintentional weight loss was defined as >5 pounds in the last 6 months or ≥2.5% of the previous year's body weight.

[b]Walking time was determined by asking participants to walk 15 feet at their usual pace.

BMI, body mass index. Nonfrail, prefrail, and frail states were defined by the presence of 0, 1–2, and ≥3 of five established criteria.

Table 2. The VACS Index

Variables	*Value*	*Points*
Age (years)	<50	0
	50–64	12
	≥65	27
CD4 (cells/mm^3)	≥500	0
	350–499	6
	200–349	6
	100–199	10
	50–99	28
	<50	29
HIV-1 RNA (copies/ml)	<500	0
	500–1×10^5	7
	≥1×10^5	14
Hemoglobin (g/dl)	≥14	0
	12–13.9	10
	10–11.9	22
	<10	38
FIB-4[a]	<1.45	0
	1.45–3.25	6
	>3.25	25
eGFR (ml/min)[b]	≥60	0
	45–59.9	6
	30–44.9	8
	<30	26
HCV infection[c]		5

[a]FIB 4 is calculated as (years of age×AST)/(platelet count×10^9/liter×square root of ALT).

[b]Estimated glomerular filtration rate is calculated as 186.3×(serum creatinine$^{-1.154}$)×(age$^{-0.203}$)×(0.742 for women)×(1.21 if black).

[c]Hepatitis C virus (HCV) infection is defined as a diagnosis with a positive antibody test or detectable virus.

VACS, Veterans Aging Cohort Study; RNA, ribonucleic acid; FIB-4, an index of liver fibrosis; eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

either a missing baseline or follow-up frailty assessment. Prior to the start of frailty assessments, 27 participants were deceased, 51 were lost to follow-up, 64 moved to another center, and 105 withdrew from the study. Compared with participants excluded from this analysis, the analysis cohort was slightly older by 1.6 years ($p=0.02$). Otherwise, the analysis cohort and the excluded participants had similar baseline characteristics.

There were 184 (61%) nonfrail, 112 (37%) prefrail, and only seven (2%) frail participants (Table 3). Prefrail/frail participants had significantly higher median VACS Index scores compared with nonfrail participants. They also had higher hepatitis C infection and lower median hemoglobin. In multivariable analysis, a higher VACS Index score was significantly associated with prefrail/frail status independent of nonwhite race, current non-full-employment, and depression (Table 4). When the components of the VACS Index were analyzed in this multivariable model, only hepatitis C infection remained associated with prefrail/frail status independent of nonwhite race, current non-full-employment, and depression (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/aid).

Participants had a median follow-up of 12 months (range, 8–16 months). The majority of nonfrail [115 of 184 (63%)]

Table 3. Comparison of the VACS Index and Its Components with Frailty Status at Baseline and at Follow-Up Assessments, the SUN Study, 2010–2012

	Baseline frailty status			*Baseline nonfrail*			*Baseline prefrail/frail*		
Characteristics	*Nonfrail* (N=*184*)	*Prefrail/ frail* (N=*112/7*)	p *value*	*Remained nonfrail* (N=*115*)	*Became prefrail/frail* N=*(68/1)*	p *value*	*Remained prefrail/frail* (N=*80/6*)	*Became nonfrail* (N=*33*)	p *value*
VACS Index	10 (6–18)	18 (10–28)	<0.001	12 (0–18)	12 (6–28)	0.017	18 (10–29)	16 (11–22)	0.263
5-year mortality risk (%)[a]	4% (3–6%)	6% (4–11%)	<0.001	4% (2–6%)	4% (3–11%)	0.017	6% (4–11%)	5.5% (4–8%)	0.263
VACS Index components									
Age (years)	48 (42–53)	48 (43–55)	0.264	48 (44–54)	49 (42–55)	0.838	49 (42–54)	49 (46–56)	0.606
CD4$^+$, (cells/mm^3)	635 (463–820)	540 (394–730)	0.010	688 (470–841)	621 (498–861)	0.910	592 (360–770)	581 (442–845)	0.794
HIV RNA <400 copies/ml, *n* (%)	168 (91%)	108 (91%)	0.870	111 (97%)	62 (90%)	0.049	78 (91%)	33 (100%)	0.070
Hemoglobin, (g/dl)	15.1 (14.3–15.9)	14.1 (12.9–15.4)	<0.001	15.3 (14.2–16.0)	14.2 (12.9–15.5)	<0.001	13.7 (12.6–15.1)	14.1 (12.8–15.4)	0.293
FIB-4	1.07 (0.81–1.44)	1.14 (0.79–1.54)	0.544	1.08 (0.82–1.43)	1.14 (0.85–1.57)	0.681	1.21 (0.89–1.59)	1.18 (0.86–1.48)	0.889
eGFR (ml/min)	88 (80–105)	93 (77–110)	0.359	90 (79–105)	94 (84–104)	0.201	94 (76–112)	101 (77–111)	0.600
Hepatitis C antibody-reactive, *n* (%)	12 (7%)	28 (24%)	<0.001	4 (3%)	8 (12%)	0.031	19 (22%)	9 (27%)	0.551

[a]Corresponding mortality risk according to the VACS Index.

All values are medians with their interquartile ranges unless otherwise specified. We used the Bonferroni method and determined that comparisons with p values <0.006 were statistically significant.

SUN Study, Study to Understand the Natural History of HIV/AIDS; VACS, Veterans Aging Cohort Study; RNA, ribonucleic acid; FIB-4, an index of liver fibrosis; eGFR, estimated glomerular filtration rate.

Table 4. Baseline Factors Independently Associated with Initial Prefrailty/Frailty Assessment on Multivariable Analysis, the SUN Study, 2010–2012

	Univariate analysis			*Multivariable analysis*		
	Odds ratio	*95% confidence interval*	p *value*	*Odds ratio*	*95% confidence interval*	p *value*
VACS Index[a]	1.037	1.019–1.055	< 0.001	1.025	1.004–1.046	0.019
Male	0.448	0.262–0.767	0.003			
Nonwhite race	2.715	1.688–4.368	< 0.001	2.140	1.217–3.763	0.008
Current not fully employed	5.110	3.010–8.674	< 0.001	2.652	1.461–4.814	0.001
Current tobacco use	1.749	1.091–2.805	0.020			
Ever tobacco use	1.709	1.027–2.843	0.039			
Alcohol use	0.382	0.235–0.621	< 0.001			
Depression	4.749	2.892–7.800	< 0.001	4.230	2.420–7.392	< 0.001
Nadir $CD4^+$ cell count[b]	0.998	0.997–1.000	0.065			
Duration of HIV infection[c]	1.060	1.012–1.111	0.015			
Current cART use	0.405	0.161–1.023	0.056			
Duration of cART use (years)[d]	1.015	0.945–1.091	0.675			
Prior opportunistic infection	1.185	0.702–2.001	0.525			

[a]Per 1 unit increase in VACS Index.
[b]Per 1 cell/mm^3 decrease in $CD4^+$ cell count.
[c]Per 1 year increase in HIV infection duration.
[d]Per 1 year increase in duration of cART use.
SUN Study, Study to Understand the Natural History of HIV/AIDS; VACS, Veterans Aging Cohort Study; cART, combination antiretroviral therapy.

and prefrail [77 of 112 (69%)] participants at baseline did not change frailty status. Conversely, the majority of frail [five of seven (71%)] participants at baseline transitioned to a prefrail status. Furthermore, among 184 nonfrail participants at baseline, 68 (37%) participants transitioned to a prefrail state compared to only one (0.5%) participant who transitioned directly to a frail state. Participants who remained prefrail/frail compared to those who remained nonfrail continued to have higher median VACS Index scores (18 versus 12, $p < 0.001$) and were more likely to have hepatitis C infection (22% versus 3%, $p < 0.001$) and a lower median hemoglobin (13.7 versus 15.3 g/dl, $p < 0.001$) (statistical comparison not shown in Table 3). Nonfrail participants who transitioned to prefrailty/frailty had lower median hemoglobin than those who remained nonfrail (14.2 versus 15.3 g/dl; $p < 0.001$). Thirty-three (28%) prefrail/frail participants transitioned to a nonfrail state. There were no major differences in the components of the VACS Index between participants who remained prefrail/frail versus those who became nonfrail. Transitions between nonfrail and prefrail/frail categories were not associated with significant changes in the VACS Index score.

Thus, we have demonstrated that HIV-related prefrailty/frailty, prevalent even among young HIV-infected persons with well-controlled HIV infection, was independently associated with a higher VACS Index. Although this association is modest, it supports the use of the VACS Index to identify HIV-infected persons with prefrailty and frailty. The high prevalence of hepatitis C infection and lower hemoglobin among prefrail and frail participants largely contributed to a higher VACS Index score in these groups.

Our findings suggest that low hemoglobin and especially hepatitis C infection could be important factors in the pathogenesis of HIV-related frailty. Both factors are associated with increased markers of inflammation, which is also characteristic of HIV-related frailty.[4] In the general population, low hemoglobin has also been directly associated with poor muscle strength and physical performance,[13] which are all part of the Fried's frailty phenotype. Hepatitis C infection was also found to independently predict development of frailty among HIV-infected and HIV-uninfected men in the recent MACS study.[3]

Our findings also highlight the contribution of race, depression, and poor social factors in the occurrence of HIV-related prefrailty/frailty. Unlike poor socioeconomic status, race has not been consistently shown to be associated with HIV-associated frailty.[14] Several studies among HIV-infected persons taking cART have shown an independent association between depression and unemployment.[3,15] The reason behind this link between race, depression, and poor social factors with HIV-associated frailty is likely multifactorial. It mirrors the strong association of low socioeconomic status with poorer health outcomes and increased all-cause mortality in the general population.[16,17]

We have also documented longitudinal changes in frailty status and correspondingly examined dynamic changes in the VACS Index. We found that the VACS Index failed to reflect transitions between nonfrail and prefrail/frail categories over 1 year. This may be because the majority of our participants had fully suppressed plasma HIV RNA, relatively robust CD4 cell counts, and little, if any, advanced renal or liver injury. Thus, using the VACS Index to monitor frailty transitions in the clinical setting may be limited.

The low sample size and number of frail participants in our study and the overall low VACS Index scores of our participants limited our analysis. Furthermore, the study was limited by the performance of only two frailty assessments during a short follow-up observation period (8–16 months). In the recent MACS study that analyzed participants who completed at least six frailty assessment visits over 4 years,

the expression of the frailty phenotype was found to be transient with almost half of the participants expressing the frailty phenotype at only one visit.[3] Of note, the Fried's frailty criteria have also not been validated among younger HIV-uninfected individuals and among HIV-infected persons.

In conclusion, we have demonstrated the association of the VACS Index with baseline prefrailty and frailty among HIV-infected persons independent of other frailty predictors. Further studies with a larger sample size, longer follow-up, and more frequent frailty assessments may be warranted to determine whether the VACS Index can be used to monitor transitions in frailty status over time. Our findings highlight the promising use of the VACS Index in the assessment of baseline frailty status within the clinical setting, and underscore its potential utility in the care of our aging HIV-infected population.

Author Disclosure Statement

No competing financial interests exist.

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